244

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EXPRESSION LEVEL AND ROLE IN URETERAL CONTRACTION OF ALPHA1-ADRENOCEPTOR SUBTYPES IN HUMAN URETER

Hypothesis / aims of study

Recently there have been some reports that tamsulosin is effective for discharge of ureter stones. The relation between voiding function of the lower urinary tract and alpha1-adrenoceptor (AR) is well known, and is applied clinically. On the other hand, there has been little research into alpha1-AR of the upper urinary tract. We studied the expression and role in ureteral contraction of alpha1-AR subtypes, which was considered to clarify the mechanism of ureteral urodymanics and passing ureter stones.

Study design, materials and methods

Specimens were taken from patients with renal cancer (n=12) or bladder cancer (n=13) who were not treated before surgery. Expression of alpha1-AR subtypes was examined by immunostain and Western blot, and each alpha1-AR subtype mRNA content was measured by quantitative RT-PCR. In the functional experiments, ureter was cut into longitudinal or spiral segments. One of these segments was suspended longitudinally in an organ bath containing Krebs solution gassed with a mixture of 95% oxygen and 5% carbon dioxide at 37C. The tissue's response was measured by means of an isometric force-transducer. Effects of silodosin (alpha1A-AR antagonist), tamsulosin (alpha1A/D-AR antagonist) and BMY-7378 (alpha1D-AR antagonist) were evaluated on phenylephrine (alpha1-AR agonist)-induced contraction, which was expressed as percentage of the maximal response.

Results

Alpha1A-AR and alpha1D-AR were detected by both immunohistochemistry and Western blot clearly. But alpha1B-AR was hardly detected. Alpha1-AR subtype mRNA by quantitative RT-PCR was alpha1d (1.00 ± 0.35) > alpha1a (0.71 ± 0.69) > alpha1b (0.14 ± 0.35) (mean ± SD, unit: 1000 copies/beta-actin). The expression levels of alpha1a and alpha1d were significantly higher than that of alpha1b ($p<0.005$). Phenylephrine concentration dependently produced contractions in isolated human ureter. Silodosin (1nM) and tamsulosin (1nM) obviously caused a rightward shift in the phenylephrine concentration response curve (Fig.1, 2). Antagonistic potencies (pK_B) of silodosin and tamsulosin were 9.84 and 10.09, respectively. On the other hand, BMY-7378 (10nM) did not show an antagonistic effect (Fig.3). It was demonstrated that alpha1A-AR antagonist was more potent than alpha1D-AR antagonist in the human ureter.

Interpretation of results

Alpha1d-AR mRNA expression is the highest among alpha1-AR subtypes in the human ureter. However, the alpha1-AR which contributed most to contraction was alpha1A-AR.

Concluding message

This is the first study about the relation between alpha1-AR and human ureter contraction. In this study, the possibility that alpha1A-AR blocking agent was useful for discharge of ureter stones was suggested. Furthermore, it seems to be important for the research into ureteral peristalsis and drug development for ureteral contraction and relaxation.

Fig.1 Antagonistic effect of silodosin in the isolated human ureter

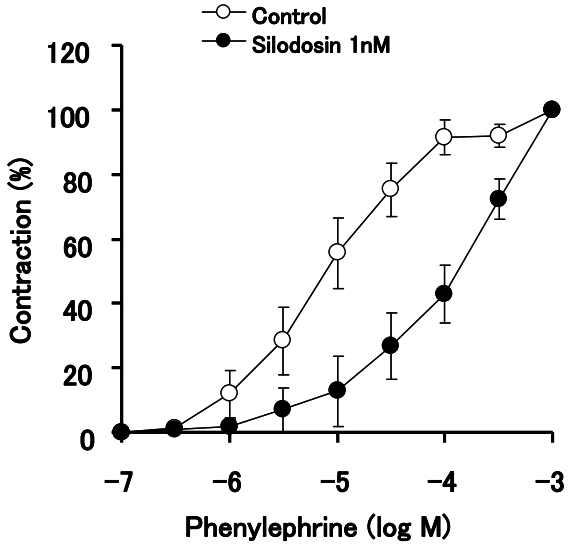


Fig.2 Antagonistic effect of tamsulosin in the isolated human ureter

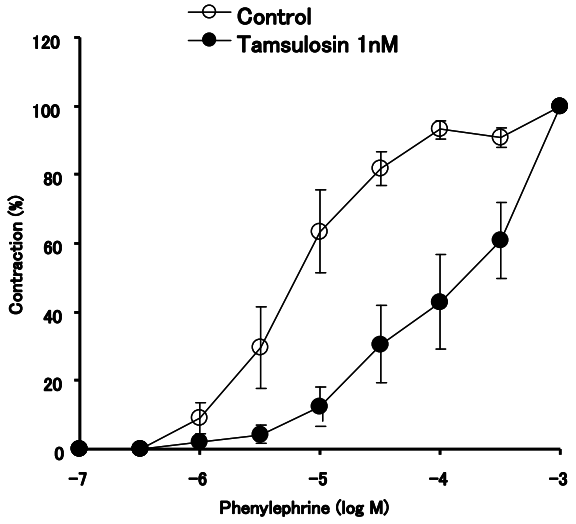
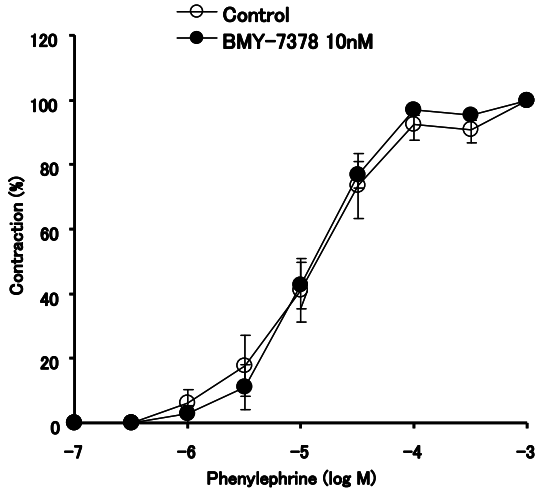


Fig.3 Antagonistic effect of BMY-7378 in the isolated human ureter



FUNDING: none

HUMAN SUBJECTS: This study was approved by the The ethics committee of Nagoya City University Graduate School of Medical Sciences and followed the Declaration of Helsinki Informed consent was obtained from the patients.